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Abstract

Objectives: Direct-acting antivirals (DAAs) are successful in curing hepatitis C virus (HCV) in over 95% of patients treated for 12 weeks. DAAs are expensive, and shortened treatment durations, which may have lower cure rates, have been proposed to reduce costs. We evaluated the lifetime cost-effectiveness of different shortened treatment durations for genotype 1 non-cirrhotic treatment-naïve patients.

Methods: Assuming a UK National Health Service perspective, we used a probabilistic decision tree and Markov model to compare three unstratified shortened treatment durations (eight, six, and four weeks) against a standard 12-week treatment duration. Patients failing shortened first-line treatment were retreated with a 12-week treatment regimen. Parameter inputs were taken from published studies.

Results: Eight weeks treatment duration had an expected incremental net monetary benefit (INMB) of £7,737 (95% CI £3,242 to £11,819) versus standard 12 weeks treatment, per 1,000 patients. Six weeks treatment had a positive INMB, although some uncertainty was observed. The probability that eight and six weeks treatment was most cost-effective was 56% and 25%, respectively, while four weeks treatment was 17%. Results were generally robust to sensitivity analyses, including a threshold analysis that showed eight weeks treatment was most cost-effective at all drug prices below £40,000 per 12-week course.

Conclusions: Shortening treatments licensed for 12 weeks to eight weeks is cost-effective in genotype 1 non-cirrhotic treatment-naïve patients. There was considerable uncertainty in the estimates for six and four weeks treatment, with some indication that six weeks treatment may be cost-effective.

Highlights

- The cost-effectiveness of direct-acting antiviral treatment for chronic hepatitis C virus has been well documented, although the cost of treatment is considerable. Shortened treatment durations have been proposed to reduce costs, albeit at the expense of potentially curing fewer patients.
- Shortening treatment duration from 12 to eight weeks using direct-acting antiviral therapy is cost-effective for treatment of mild chronic hepatitis C virus in genotype 1 non-cirrhotic treatment-naïve patients, provided a retreatment strategy is adopted for patients that fail first-line treatment.
- There was considerable uncertainty in the cost-effectiveness estimates for six and four weeks shortened treatment, with some indication that six weeks treatment may be cost-effective, but that four weeks treatment may not be cost-effective. More robust evidence on the efficacy of six and four weeks shortened treatment durations is needed.

Introduction

The cost-effectiveness of direct-acting antiviral (DAA) treatment for chronic hepatitis C virus (HCV) has been well documented [1-4], and a wide array of DAA therapies have been approved for use internationally [5]. The therapies, which are generally administered orally over 12 weeks, are successful in over 95% of patients with chronic HCV genotype 1 (GT1) [5]. The advent of an effective cure has brought the potential to address HCV globally. The World Health Organisation (WHO) recently outlined its commitment towards eliminating HCV by 2030 [6]. However, the cost of a standard 12-week treatment course is high, and variations in price exist internationally and across DAA regimens. In the UK, the price set by manufacturers initially ranged from £30,000 to £60,000 per patient [7-9], whereas in the US, a 12-week course of treatment can cost more than $90,000 per patient [10]. Although significantly lower prices have been agreed between manufacturers and health care payers, these prices have not been made publicly available. Shortened treatment duration is one mechanism that could be used to reduce drug costs, albeit at the expense of potentially curing fewer patients.

Recent evidence suggests shortened treatment durations are associated with lower cure rates in GT1 non-cirrhotic treatment-naïve patients. Kowdley et al. [11] reported that the cure rate fell from 96% in patients treated for 12 weeks using a triple DAA regimen (ombitasvir-paritaprevir-ritonavir with dasabuvir (3D)) to 88% in patients treated for eight weeks with the same regimen. Sulkowski et al. [12] considered shorter treatment durations using a combination of four DAAs (daclatasvir, asunaprevir, beclabuvir, and sofosbuvir (DCV-Trio + SOF)) and found 57% and 29% of patients treated over six and four weeks, respectively, cleared the virus. Other studies considered the effectiveness of existing DAA therapies over shortened treatment durations, but with the addition of an investigational non-nucleoside or

protease inhibitor. For example, Kohli et al. [13] found 40% of patients were cured when treated for four weeks using ledipasvir and sofosbuvir (LDV/SOF) plus a non-nucleoside inhibitor (GS9669).

Although cure rates are lower over shortened treatment durations, patients can usually be retreated with an alternative, or similar, DAA regimen if first-line treatment fails. One concern with first-line treatment failure, however, is patients can develop resistance to DAA therapies and this can affect the likelihood of future viral eradication [14]. However, much evidence suggests non-cirrhotic patients with DAA resistance, or resistance-associated polymorphisms, can clear the virus with further treatment [15-19] even before the advent of combinations with broader antiviral activity. Wilson et al. [19] found 90% of patients with DAA resistance were cured with 12 weeks retreatment using LDV/SOF, while 91% of patients overall were cured, following shortened first-line treatment failure. Bourliere et al. [20] found 97% of patients that previously failed first-line treatment cleared the virus over 12 weeks using sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX).

Given the burden of high treatment costs, and the potential to cure as many patients using shortened treatment durations (with a retreatment strategy adopted for all patients that fail first-line treatment), the cost-effectiveness of short-course therapy needs to be considered. In this paper, we compared the lifetime cost-effectiveness of different unstratified shortened treatment durations. We modelled outcomes for GT1 non-cirrhotic treatment-naïve patients with HCV in the UK, for whom shortened treatment has been reported in the literature, and for whom shortened treatment may be considered in the future.

Methods

We used a decision tree and Markov model to investigate the cost-effectiveness of shortened DAA treatment from the National Health Service (NHS) perspective in the UK. We applied

monthly cycles during the first year in the decision tree to simulate treatment outcomes and annual cycles in the Markov model to simulate the natural history of HCV. We adopted a lifetime time horizon (60 years, from an initial age of 40) and discounted costs and utilities at 3.5% per annum, as per NICE guidelines [21].

Target population

The model simulated outcomes for GT1 non-cirrhotic treatment-naïve patients infected with HCV, combining data from sub-types 1a and1b. We modelled outcomes for a representative population with non-cirrhotic HCV in the UK, based on Hartwell et al. [22]. At baseline, 51.1% and 48.9% of patients had mild (F0-F1) and moderate (F2-F3) liver fibrosis, respectively. At model entry, patients were aged 40 years and 70% were male (Table 1).

Treatment comparators and regimens

We compared three unstratified shortened treatment durations (eight, six, and four weeks) against the standard 12-week treatment duration. We considered treatment regimens currently used in the UK in our analysis. In the base case analysis, we used a triple-DAA regimen (3D) for first-line treatment due to the availability of data on the effectiveness of shortened treatment [11]. 3D contains two fixed-dose tablets with 12.5mg ombitasvir, 75mg paritaprevir, and 50mg ritonavir, which are taken daily along with one-dose 250mg dasabuvir [8].

We assumed patients that failed first-line treatment were retreated for 12 weeks, as per recent UK guidelines [23, 24]. We used SOF/VEL/VOX as the salvage regimen. SOF/VEL/VOX is a non-structural protein 5A (NS5A) inhibitor-containing regimen that is administered once daily using a fixed-dose tablet; each tablet contains 400mg sofosbuvir, 100mg velpatasvir (NS5A inhibitor) and 100mg voxilaprevir (protease inhibitor) [25]. SOF/VEL/VOX is the

currently recommended treatment regimen for patients that previously failed first-line treatment in the UK [23, 24].

Model structure

The decision tree was designed to capture treatment outcomes in the first year using monthly cycles (Figure 1a). Patients were assessed for sustained virological response at 12 weeks post treatment (SVR12, effective cure), which was defined as having HCV ribonucleic acid (RNA) less than 25 IU per millilitre. Patients that failed first-line treatment were retreated at 24 weeks. All patients entered the Markov model based on their response to treatment.

The Markov model was adapted from previously validated models that characterise the natural disease history of HCV [3, 22, 26, 27]. Patients entered the model based on their initial distribution of liver fibrosis (mild or moderate), and whether treatment had been successful (Figure 1b). In HCV-cleared patients, we modelled potential reinfection. Patients without SVR12 could progress from mild (F0-F1) to moderate (F2-F3) to severe liver fibrosis, or compensated cirrhosis (F4). Once in this health state, patients could develop more advanced liver disease, including hepatocellular carcinoma and decompensated cirrhosis. Patients with decompensated cirrhosis were also at risk of hepatocellular carcinoma, with both groups of patients at risk of requiring a liver transplant. We modelled liver-related deaths for each of these advanced health states with two health states captured in the hepatocellular carcinoma and liver transplant health states to reflect the initial and subsequent risk of liver-related mortality. At any stage in the Markov model, patients could die from non-liver-related deaths.

Model assumptions

We assumed there was no progression to more severe health states during treatment, such as compensated cirrhosis (F4), or once treatment had been successful. Only if patients became re-infected could disease progression occur. There are no clinical guidelines on the appropriate length of time patients should wait before a salvage treatment is administered. In our model, we assumed the wait time did not affect the success of retreatment.

Parameter inputs

We informed the model using a synthesis of evidence, as summarised in Table 1 and described below.

Treatment-related inputs

We synthesised evidence from two sources to inform the efficacy of first-line 3D treatment. Kowdley et al. [11] reported SVR12 for 3D following 12 and eight weeks treatment, based on a large phase 2b clinical trial with 571 patients, and found 96% and 88% of patients, respectively, cleared the virus. Evidence on shorter treatment durations for 3D were not available, however, SVR12 for an alternative DAA regimen using DCV-Trio + SOF was reported by Sulkowski et al. [12] for a similar population following six and four weeks treatment. The small phase 2 clinical trial with 28 patients reported that 57% and 29% of patients achieved SVR12 following six and four weeks treatment, respectively. For our analysis, we assumed the odds ratio of SVR12 following six and four weeks treatment using DCV-Trio + SOF could be applied to 3D. We calculated the odds ratio of available data (i.e., eight versus 12 weeks and four versus six weeks), averaged these to estimate eight versus six weeks, and applied these to our baseline 3D estimates to obtain predicted estimates for six and four weeks for 3D therapy. We used a Bayesian Markov chain Monte Carlo (MCMC)

simulation framework to pool the evidence to propagate and reflect the uncertainties in these estimates for use in probabilistic sensitivity analysis (see Appendix 1 for further details). The estimated SVR12 was 96%, 87%, 64%, and 38% following 12, eight, six, and four weeks treatment, respectively, with uncertainty around these estimates given in Table 1.

Bourliere et al. [20] provided evidence on the efficacy of retreatment using SOF/VEL/VOX from two phase 3 clinical trials (POLARIS-1 and POLARIS-4). Overall, 97.3% of patients achieved SVR12; we used this parameter to inform the expected SVR12 in patients that failed any of the treatment strategies. We assessed uncertainty in this parameter using data obtained from Bourliere et al. [20] and beta distributions.

Treatment-related adverse events associated with DAA treatment were modelled to reflect the potential impact of these clinical events over different treatment durations. We obtained the probability of adverse events occurring from a clinical trial of 3D treatment, as reported by Johnson et al. [3]. To estimate the probability of these events occurring over different treatment durations, we converted the probabilities to rates and calculated the time-dependent probability for each strategy (Appendix 2). We assumed the probability of adverse events occurring was the same for retreatment as for first-line treatment. The adverse events included anemia, rash, depression, grade 3 or 4 neutropenia, and grades 3 or 4 thrombocytopenia.

Epidemiological inputs

The Markov model simulated the natural disease history of HCV using annual transition probabilities, which are presented in Table 1. We derived estimates from published studies on the probability of reinfection (1% per annum) [3], fibrosis [28, 29] and non-fibrosis [30, 31] progression, liver-related mortality [28, 31, 32], and all-cause mortality, stratified by age and sex [33].

Costs

The model considered both treatment-related and health state costs from the perspective of the NHS in the UK (Table 1). All unit costs were expressed in Sterling (£) and valued at 2016/17 prices.

The costs for the drug regimens were taken from the respective NICE technology appraisals for 3D [8] and SOF/VEL/VOX [25] (Table 1). These costs were applied on a pay-per-tablet basis, rather than pay-per-treatment success basis. We also considered monitoring costs, and derived these from a previous technology appraisal for a similar DAA [7]. We assumed monitoring costs were the same for first-line treatment and retreatment, as these costs were not expected to vary by DAA treatment. Treatment-related costs (drug and monitoring costs) were assumed to be fixed in the model as these prices were not expected to vary in the UK. The costs associated with adverse events were taken from Johnson et al. [3]. We assessed uncertainty in these estimates using gamma distributions.

Health state costs were derived from a previous UK evaluation of HCV by Hartwell et al. [22] and a cost analysis of resource use incurred by both HCV-infected and -cleared patients, undertaken by Backx et al. [34]. Gamma distributions were assumed for all cost inputs. We updated costs to 2016/17 prices using the Hospital and Community Health Services (HCHS) index [35] (Table 1).

Utility weights

We derived treatment-related and health state utility estimates from published studies (Table 1). Johnson et al. [3] provided treatment-related utilities for 3D treatment. The quality of life estimates were obtained from the EQ-5D-5L questionnaire, which was administered to

patients participating in clinical trials for 3D treatment. For our analysis of shortened treatment, we converted the 12-week treatment estimates to reflect the monthly deterioration in quality of life due to adverse events associated with treatment. We assumed the same treatment-related utilities for SOF/VEL/VOX as these have not yet been published.

Health state utilities for HCV infection were derived from Wright et al. [29], and reflected the expected annual health-related quality of life associated with each HCV health state. As in Wright et al. [29], and other analyses [3, 22], we assumed the health utility associated with treatment success (SVR12) was greater than the baseline utility level by a score of 0.05 for both mild and moderate liver fibrosis. We assumed the health utility in successfully treated patients was fixed in the model. We investigated uncertainty in infected patients using beta distributions (Table 1).

Cost-effectiveness analyses

Base case analysis

The base case analysis compared the lifetime cost-effectiveness of different shortened treatment durations against the standard 12-week treatment duration for GT1 non-cirrhotic treatment-naïve patients in the UK. We calculated expected costs and quality-adjusted life years (QALYs) per 1,000 patients using a probabilistic analysis, with parameters sampled from predefined distributions over 10,000 simulations in Microsoft Excel software [36]. The expected costs and QALYs were computed as an average over the 10,000 simulations. We calculated the expected incremental net monetary benefit (INMB) of each shortened treatment strategy relative to 12 weeks treatment, assuming £20,000 willingness-to-pay (WTP):

$$\text{Expected INMB} = (Expected\ QALYs) * £20{,}000 - (Expected\ costs)$$

We also calculated the expected cost per cure:

$$\text{Cost per cure} = \frac{cost[duration]}{pCured[duration]}$$

where *pCured* is the proportion of patients cured over the treatment duration. We reported the probability that any strategy was the most cost-effective treatment strategy at different WTP thresholds using cost-effectiveness acceptability curves.

Sensitivity analyses

We considered alternative DAA regimens currently used in the UK as first-line treatment to assess the impact of different drug prices and utility scores on cost-effectiveness. These included LDV/SOF, daclatasvir plus sofosbuvir (DCV/SOF), and elbasvir/grazoprevir (ELB/GZR). (The cost and utility estimates used in these analyses are detailed in Appendix 3.)

We assessed the impact on cost-effectiveness of lower drug prices. The base case analysis used prices reported in the NICE technology appraisals, however, reduced drug prices were agreed by the drug manufacturers and NICE, which have not been made publicly available. In a sensitivity analysis, we reduced drug prices by 80% (to £7,284.34 and £8,965.40 per 12-week course for first-line treatment and retreatment, respectively). We considered alternative discount rates in sensitivity analyses to assess the impact of lower (1.5%) and higher (5%) discount rates on cost-effectiveness findings. This was useful to assess the generalisability of our findings to other health care settings where different discount rates are applied. Here, we assumed the same 80% reduction in drug prices.

Scenario analyses

Due to uncertainty in the cost of treatment in the UK and elsewhere, we used a threshold analysis to investigate cost-effectiveness under different drug prices. Here, we ranged the cost from zero to £40,000 per 12-week course for both first-line treatment and retreatment simultaneously.

We also used threshold analyses to investigate the impact of different first-line cure rates on cost-effectiveness for each shortened treatment strategy separately, assuming the same 80% reduction in drug prices. First, we considered higher SVR rates for eight weeks treatment, holding all else constant, as the base case rate of 87% was somewhat conservative; higher success rates over eight weeks have been reported for other regimens [37], as well as newer DAAs [38]. In this scenario, we ranged SVR12 between 86% and 96%. Following six weeks treatment, we varied the first-line cure rate between 40% and 85% (i.e., between the SVR12 following four (38%) and eight (87%) weeks treatment), holding all else constant. Lastly, we investigated the cost-effectiveness of four weeks treatment at higher cure rate thresholds, constrained at 65% (i.e., constrained at the SVR12 following six weeks treatment).

Due to some uncertainty in the cure rate following retreatment, we conducted a threshold analysis on this parameter also. Here, we varied the cure rate between zero and 100% and assumed the same thresholds for each shortened treatment strategy. We assumed the same 80% reduction in drug prices in this scenario also.

Results

Base case findings

Eight weeks treatment generated lower expected lifetime costs and fewer QALY gains compared with 12 weeks treatment. The strategy had the lowest expected lifetime cost per

cure at £32,607 (95% CI £29,288 to £36,699). At £20,000 WTP, despite the smaller QALY gains, the strategy had the highest INMB per 1,000 patients at £7,737 (95% CI £3,242 to £11,819) due to the considerable cost savings associated with the shortened treatment strategy (Table 2). At 56%, the strategy had the highest probability of being the most cost-effective option. Six weeks treatment produced a positive expected INMB, although some uncertainty was observed due to imprecise estimates on the effectiveness of shortened treatment (INMB £1,860 (95% CI £-14,517 to £15,153)). The strategy had a lower probability of being most cost-effective at 25%. Similar uncertainty was observed in the four-week treatment strategy, which produced a negative expected INMB (£-4,735 (95% CI £-24,197 to £20,141)) due to higher overall lifetime costs and lower QALY gains. The strategy had 17% probability of being most cost-effective.

Sensitivity analyses findings

Changing the drug regimen for first-line treatment did not affect the base case findings, except in the case of the four-week treatment strategy which produced a positive INMB using DCV/SOF as first-line treatment. The main driver for this change was the increased cost of first-line treatment, which increased the overall cost of 12 weeks treatment. In all cases, the eight- and six-week treatment strategies produced a positive expected INMB (Appendix 3). Greater uncertainty was observed when DCV/SOF was used as first-line treatment, however, the shortened treatment strategies had comparably higher probabilities of being the most cost-effective treatment strategies compared to 12 weeks treatment (Appendix 3).

Reducing drug costs by 80% introduced some uncertainty in the results. Due to the reduced cost-saving, the eight weeks treatment strategy returned a considerably smaller INMB with some uncertainty observed (£1,370 (95% CI £-344 to£2,685)). However, the strategy still had

the highest probability (47%) of being most cost-effective due to lower expected lifetime costs (Table 2; CEAC presented in Appendix 4).

The results were robust to changes in the discount rate (Appendix 5). At the lower rate of 1.5%, the same uncertainty was observed, and the eight-week strategy still had the highest probability of being most cost-effective, at 46%. At the higher rate of 5.0%, the probability that eight weeks treatment was most cost-effective increased to 50% and no uncertainty in the expected INMB was observed.

Scenario analyses findings

Figure 2 presents the findings from the drug-cost threshold analysis. The results are plotted using information on the probability of cost-effectiveness at £20,000 WTP. The horizontal axis presents the different drug costs. At zero drug costs, 12 weeks treatment was the most cost-effective option due to the obvious QALY advantage over the shortened treatment strategies. However, eight weeks treatment had the highest probability of being most cost-effective at all drug costs above zero due to the available cost-savings. At all prices above £6,000 per 12-week course, six weeks treatment had a consistently higher probability (>20%) than 12 weeks treatment of being most cost-effective. Four weeks treatment had consistently low (<20%) probability of being the most cost-effective strategy at all drug prices.

Figure 3 presents the findings from the first-line cure rate threshold analysis following eight, six, and four weeks treatment, respectively. The results are similarly plotted using information on the probability of cost-effectiveness. The probability that eight weeks treatment duration is cost-effective increases with each percentage increase in SVR12 (Figure 3a). At 96% SVR12, *ceteris paribus*, the probability that the strategy is most cost-effective is 60%. If SVR12 following six weeks treatment was 77% or higher, *ceteris paribus*, the strategy had the highest probability of being the most cost-effective strategy (Figure 3b). Four

weeks treatment had lowest probability of being most cost-effective, even when SVR12 was as high as 65% (Figure 3c).

The results from the retreatment cure rate threshold analysis are presented in Figure 4. At retreatment cure rates above 65%, eight weeks treatment had the highest probability of being the most cost-effective strategy. Six and four weeks treatment had a higher probability of being cost-effective compared with 12 weeks treatment if SVR12 following retreatment was 92.5% and 97.5% or higher, respectively.

Conclusions

We compared the lifetime cost-effectiveness of three unstratified shortened treatment durations (eight, six, and four weeks) against 12 weeks treatment, with a retreatment strategy adopted for all patients that failed first-line treatment, for GT1 non-cirrhotic treatment-naïve patients in the UK. Eight weeks treatment generates marginally fewer expected lifetime QALYs than standard 12 weeks treatment duration, but is the most cost-effective option due to considerably lower expected lifetime costs arising from lower first-line treatment costs. There is considerable uncertainty surrounding the cost-effectiveness of six and four weeks treatment due to limited evidence on efficacy, although there is some indication that six weeks treatment may be cost-effective, while four weeks treatment is likely not cost-effective.

Provided drug costs are above zero, eight weeks treatment has the highest probability of being most cost-effective due to the available cost-savings versus standard 12 weeks treatment duration. Six weeks treatment had a higher probability than 12 weeks treatment of being most cost-effective at all drug prices above £6,000 per 12-week course, however, the probability was generally low at ~30%. Eight weeks treatment is highly cost-effective at higher first-line cure rates; at 96% SVR12, the strategy has 60% probability of being most

cost-effective. Six weeks treatment would be the most cost-effective option if the first-line cure rate was 77% or higher, while four weeks treatment always had a low probability of being most cost-effective, even when the first-line cure rate was as high as 65%. Shortening treatment duration is cost-effective if the retreatment cure rate is 65% or higher following eight weeks treatment, or 92.5% and 97.5% following six and four weeks treatment, respectively.

Discussion

Strengths and limitations

This is the first study to consider the cost-effectiveness of short-course therapy for chronic HCV, to the best of our knowledge. We compared three different shortened treatment durations using data reported in the literature for a non-cirrhotic treatment-naïve population. We developed a decision tree to capture treatment outcomes and adapted a previously validated Markov model to reflect the disease history of HCV. We assessed a number of DAA regimens currently used in the UK and conducted a variety of sensitivity and scenario analyses. Our results were generally robust to these analyses.

There are limitations to this work. The evidence on the effectiveness of shortened treatment duration is limited, and often limited to DAAs not currently approved. With the exception of Kowdley et al. [11] who reported the effectiveness of 3D treatment, which is currently recommended for use internationally, the majority of studies considered the effectiveness of a combination of DAA regimens [12], or explored the effectiveness of existing DAA regimens but with the addition of an investigational non-nucleoside or protease inhibitor, for example [13, 39, 40]. As a consequence, these analyses have had little impact on policy. For instance, in the UK, the recommended standard treatment duration for all DAA regimens in GT1 is 12-16 weeks, with the exception of LDV/SOF which is recommended for use over eight weeks

in patients with low baseline viral load, and glecaprevir/pibrentasvir which is a new regimen that is licensed for use over eight weeks[41]. Although the evidence is limited, we used Kowdley et al. [11] as our baseline source for efficacy data on 12 and eight weeks treatment and predicted the expected cure rate for this regimen over six and four weeks duration using data from Sulkowski et al. [12].

The evidence for the effectiveness of retreatment is also limited, although the majority of studies report considerably high success rates in GT1 non-cirrhotic patients [15, 17-20, 42]. For our analysis, we used recent evidence from Bourliere et al. [20] who investigated the effectiveness of retreatment using the now currently recommended retreatment regimen (SOF/VEL/VOX) over 12 weeks for a similar non-cirrhotic population that fail first-line therapy. In scenario analysis, we assessed lower retreatment cure rates and found the shortened treatment strategies were more cost-effective than 12 weeks treatment provided SVR12 following retreatment was 65% or higher following eight weeks treatment, and 92.5% and 97.5% following six and four weeks treatment, respectively.

Although the cost of DAA treatment is high, we do not know the actual price health care payers pay for these drugs. In our base case analysis, we assumed the prices reported in the technology appraisals [7-9, 43], which are an exaggeration of the actual prices paid. In a threshold analysis, we varied these prices and found the base case findings remained generally robust at prices below £40,000 per 12-week course.

Finally, we took a UK perspective in this paper. Although some variations in monitoring costs might exist internationally, there is little to differentiate in terms of treatment costs, patient outcomes, and disease progression. Discount rates differ across some settings; for instance, in Australia, Estonia, Latvia, Lithuania, and Ireland, the applied discount rate is 5%, while in Canada it is 1.5% [44]. We applied these rates in sensitivity analyses and found the

results remained generally unchanged, suggesting our findings may be generalisable to other health care settings that assume the same, or either lower or higher discount rates. The findings are also likely generalisable across DAA regimens, which are generally homogenous; DAAs have similar cure rates, comparably high treatment costs, and impact patient's quality of life uniformly. We did not explore strategies that might stratify patients as suitable for shortened therapy at four and six weeks, though such approaches are likely to improve the cost-effectiveness of treatment.

Implications for practice

Our findings that eight or even six) weeks shortened treatment duration is likely to be cost-effective are important in the context of clinical practice. Treating patients over shortened durations in resource-constrained settings, for example, allows scarce resources, such as staff, to be better allocated and distributed although such approaches need to be balanced against the complexity of delivering care. The decision to treat patients, particularly those with high loss to follow up, such as chaotic drug users, is also less problematic. Treating these patients over shortened treatment durations is effective and cost-effective if a salvage treatment can be administered. This may be useful in settings where there is a limited time available for treatment, e.g. prisons; however, the decision to treat patients serving short sentences remains problematic due to loss to follow up. Future research should identify the potential cost-effectiveness of shortened treatment durations in this context.

Although short-course therapy is not currently recommended, the cost-effectiveness of this approach is clear. Shortening treatment to eight or six weeks using existing DAA therapies, such as 3D, LDV/SOF, DCV/SOF, and ELB/GZR appears cost-effective, although some uncertainty in the six-week treatment strategy exists. We highlight the need for further evidence on the efficacy of six and four weeks treatment using licensed regimens, along with

evidence on the success of retreatment. Future research should also identify patients for whom shortened treatment is likely to be effective, with treatment duration optimised based on baseline viral load or resistance to DAA therapies, for example, which has been shown to limit patients chance of viral eradication [45, 46], particularly in those with prolonged exposure to treatment previously [15].

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Table 1 Summary of treatment, epidemiological, cost, and quality of life inputs for probabilistic sensitivity analyses

Variable	Base case	Distribution	Alpha	Beta	Source
Patient characteristics					
Initial distribution of liver fibrosis					
Mild (F0-F1)	51.1%	-	-	-	[22]
Moderate (F2-F3)	48.9%	-	-	-	[22]
Age	40	-	-	-	[22]
Male	70%	-	-	-	[22]
Efficacy (SVR12)					
First-line treatment					
12 weeks	0.96	Beta	76	3	[11]
8 weeks	0.87	Beta	69	10	[11]
6 weeks	0.64	Beta	6	3	[12][a]
4 weeks	0.38	Beta	1	2	[12][a]
Retreatment					
12 weeks	0.91	Beta	31	3	[19]
Annual transition probabilities					
Fibrosis progression					
Mild-to-moderate	0.025	Beta	38	1484	[28, 29]
Moderate-to-CC	0.037	Beta	27	699	[28, 29]
Non-fibrosis progression					
CC-to-DCC	0.039	Beta	15	359	[31]
CC-to-HCC	0.014	Beta	2	135	[30]
DCC-to-HCC	0.014	Beta	2	135	[30]
HCC-to-liver transplant	0.020	Beta	98	4801	[22]
DCC-to-liver transplant	0.020	Beta	98	4801	[28]
Liver-related mortality					
DCC-to-liver death	0.130	Beta	147	983	[31]
HCC-to-liver death (first year)	0.430	Beta	117	155	[31]
HCC-to-liver death (subsequent year)	0.430	Beta	117	155	[31]
Liver transplant-to-liver death (first year)	0.150	Beta	85	481	[28]
Liver transplant-to-liver death (subsequent year)	0.057	Beta	85	1407	[32]
Reinfection	0.010	Beta	4	391	[3]
Costs					
Treatment-related costs					
3D (monthly)	£12,140.56	Fixed	-	-	[8]
SOF/VEL/VOX (monthly)	£14,942.33	Fixed	-	-	[25]
Monitoring costs (monthly)	£162.34	Fixed	-	-	[7]
Health state costs					
SVR Mild (F0-F1)	£60.36	Gamma	34	2	[34]
SVR moderate (F2-F3)	£60.36	Gamma	34	2	[34]
Mild (F0-F1)	£166.50	Gamma	13	13	[22]
Moderate (F2-F3)	£612.50	Gamma	35	17	[34]
CC (F4)	£951.13	Gamma	17	54	[34]
DCC	£12,833.96	Gamma	15	849	[22]
HCC (first year)	£11,436.41	Gamma	13	894	[22]
HCC (subsequent year)	£11,436.41	Gamma	13	894	[22]
Liver transplant (first year)	£51,769.79	Gamma	15	3473	[22]
Liver transplant (subsequent year)	£1,949.08	Gamma	14	136	[22]
Adverse event costs					
Anemia	£501.58	Gamma	10	48	[3]
Rash	£166.50	Gamma	16	10	[3]

Depression	£414.17	Gamma	16	26	[3]
Neutropenia	£980.26	Gamma	10	98	[3]
Thrombocytopenia	£875.16	Gamma	14	62	[3]
Utilities					
Treatment-related utilities (penalties)					
Mild (F0-F1) - 3D (monthly)	-0.001	Fixed	-	-	[3]
Moderate (F2-F3) - 3D (monthly)	-0.001	Fixed	-	-	[3]
Health state utilities					
SVR mild (F0-F1)	0.820	Fixed	-	-	[29]
SVR moderate (F2-F3)	0.710	Fixed	-	-	[29]
Mild (F0-F1)	0.770	Beta	141	42	[29]
Moderate (F2-F3)	0.660	Log-normal	-	-	[29]
CC (F4)	0.550	Log-normal	-	-	[29]
DCC	0.450	Beta	55	67	[29]
HCC (first year)	0.450	Beta	55	67	[29]
HCC (subsequent year)	0.450	Beta	55	67	[29]
Liver transplant (first year)	0.450	Beta	55	67	[22]
Liver transplant (subsequent year)	0.670	Beta	32	16	[29]

[a] Synthesised from Kowdley et al. [11] and Sulkowski et al. [12]: see Appendix 1 for further details.

SVR12, sustained virological response at 12 weeks; CC, compensated cirrhosis; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; 3D, ombitasvir, paritaprevir ritonavir with dasabuvir; SOF/VEL/VOX; sofosbuvir/velpatasvir/voxilaprevir; DCV-Trio + SOF, daclatasvir, asunaprevir, beclabuvir and sofosbuvir

Table 2 Cost-effectiveness findings

	Costs (95% CI)	QALYs (95% CI)	Cost per cure (95% CI)	INMB (95% CI)[a,b]	p(CE)[b]
Base case analysis					
12 weeks	£40,911 (£38,742 to £44,007)	15.51 (15.00 to 16.16)	£41,051 (£38,788 to £44,313)	-	0.029
8 weeks	£32,821 (£29,513 to £36,971)	15.49 (14.98 to 16.14)	£33,194 (£29,701 to £37,669)	£7,737 (£3,242 to £11,819)	0.558
6 weeks	£37,668 (£25,511 to £52,476)	15.44 (14.92 to 16.11)	£39,048 (£25,746 to £56,050)	£1,860 (£-14,517 to £15,153)	0.245
4 weeks	£43,126 (£20,506 to £59,551)	15.38 (14.83 to 16.07)	£46,021 (£20,762 to £67,835)	£-4,735 (£-24,197 to £20,141)	0.168
Sensitivity analysis (80% reduction in drug prices)					
12 weeks	£11,455 (£9,951 to £13,657)	15.51 (14.99 to 16.16)	£11,495 (£9,972 to £13,721)	-	0.220
8 weeks	£9,738 (£8,083 to £12,016)	15.49 (14.97 to 16.14)	£9,848 (£8,136 to £12,217)	£1,370 (£-344 to £2,685)	0.470
6 weeks	£10,892 (£7,617 to £14,835)	15.44 (14.9 to 16.11)	£11290 (£7,709 to £15,949)	£-815 (£-6,868 to £3,170)	0.203
4 weeks	£12,203 (£6,634 to £17,020)	15.38 (14.82 to 16.07)	£13,008 (£6,706 to £19,512)	£-3,197 (£-12,090 to £4,291)	0.107

[a] Versus 12 weeks

[b] At £20,000 willingness-to-pay

QALYs, quality-adjusted life years; INMB, incremental net monetary benefit; p(CE), probability most cost-effective; CI, confidence interval

Figure 1 Economic model structure
(a) Decision tree simulating treatment outcomes
(b) Markov model simulating natural disease history

Figure 2 Probability of cost-effectiveness at £20,000 willingness-to-pay and different drug costs

Figure 3 Probability of cost-effectiveness at £20,000 willingness-to-pay and different first-line cure rate thresholds
(a) Eight weeks treatment
(b) Six weeks treatment
(c) Four weeks treatment

Figure 4 Probability of cost-effectiveness at £20,000 willingness-to-pay and different retreatment cure rate thresholds

Supplementary material

Appendix 1 – Calculating SVR12 by treatment duration

Appendix 2 – Probability of adverse events

Appendix 3 – Sensitivity analyses with alternative DAA regimens

Appendix 4 – Sensitivity analysis with 80% reduction in drug prices

Appendix 5 – Sensitivity analysis with lower (1.5%) and higher (5.0%) discount rates